REMARKS

After the above amendments, claims 1, 2, 5, 6, 9-19, 26-29, 31, 32, 53 and 55-57 are pending.

Further Copies of IDS References Not Required

Rule 98(d) (*i.e.*, 37 CFR §1.98(d)) was in force as of the present application's filing date and clearly stated that copies of references listed in an IDS need not be provided if the references were already submitted in conjunction with a properly identified parent application. Thus, in the present case, further copies of the IDS references are not required. Applicant respectfully requests that the Examiner now consider the references.

Double Patenting

Applicant notes with appreciation the Examiner's deferral of the provisional obviousness-type double patenting rejection.

Written Description

The rejection under 35 USC 112, first paragraph, for allegedly lacking adequate written description is moot in view of the present amendment. The Office action had asserted that "one in the art would not recognize that the structural features that allow binding of a vast array of arylpropionic acids to a wide array of proteins, serum protein, or vascular protein have been adequately described." This was based on a determination that "one species is inadequate."

The Office action appeared to embrace the notion that only serum albumin is sufficiently described. However, the Examiner is reminded that the Office action attempted to use Applicant's list of drugs which reversibly bind to plasma proteins (page 14, line 24 to page 15, line 6) as an "admission" to establish an obviousness rejection, along with Clin. Pharmacokinet. 26 (1):44-58, 1994 ("Herve") and Fundam. Clin. Pharmacol. 1998: 12:286-291 ("Lagrange"), which also discuss binding. As the Office action has cited no evidence to contradict the sufficiency of Applicant's list, *and to the contrary has used references to demonstrate what was known to those skilled in the art*, Applicant believes there can be no written description rejection regarding plasma proteins. Applicant clearly had possession of the full scope of the invention as now claimed.

Enablement

Claims "1, 2, 5-19, 21-29, 31, 32, 34-44, 46, and 48-57" were rejected under 35 USC 112, first paragraph for allegedly lacking enablement. Claims 21-25, 34-38, 44, and 48-52 were canceled in the Applicant's response dated November 25, 2002. Applicant traverses the rejection with respect to the claims that are pending, where the rejection has not been rendered moot by amendment.

The Office action dated October 3, 2001, (and incorporated by reference by the current Office action) mentioned that the originally filed claims were only enabled for arylpropionic acids that are ibuprofen and that bind to serum albumin. Of course, this is unnecessarily narrow. The evidence presented by the Office action appears to surround the mechanics of protein binding (*e.g.*, section c.). However, as noted above, the Examiner has

already demonstrated that plasma proteins are known to bind arylpropionic acids. The mechanics of such binding need not be considered.

Applicant has exemplified numerous arylpropionic acid-oligonucleotide conjugates. Such conjugates are claimed in independent claims 5 and 29, and since these claims do not refer to protein, the rejection based on the unpredictability of protein binding is improper as applied to them. Applicant requests that the rejection be withdrawn.

Applicant stresses that the key "undue experimentation" criterion cannot be met with regard to the amended claims. To the extent that experimentation would be required, the Office action's standard of "undue trial and error experimentation" is not proper. The Examiner is reminded that "time and difficulty of experiments are not determinative if they are merely routine." MPEP 2164.06. Likewise, "the fact that experimentation may be complex does not necessarily make it undue." MPEP 2164.01. Applicant has provided more than ample direction to those skilled in the art to make and use the invention.

Anticipation

Claims 1, 2, 7-11, 13-19, and 26-28 stand rejected under 35 USC 102(b) as anticipated by U.S. Patent No. 5,607,691 ("Hale"). Amendments have rendered the rejection moot. Hale fails to teach all limitations of the independent claims 1 and 26 as amended, and thus cannot support an anticipation rejection.

Obviousness

Claims 1, 2, 5-11, 13-19, 26-29, 31, 32, 39, 40, and 55-57 stand rejected under 35 USC 103(a) as obvious over a combination of Hale, U.S. Patent No. 4,973,745 ("Blaschke"), Clin. Pharmacokinet. 26 (1):44-58, 1994 ("Herve"), Fundam. Clin. Pharmacol. 1998: 12:286-291 ("Lagrange"), Applicant's specification (page 14, line 21- page 15, line 3), and U.S. Patent No. 5,714,142 ("Blaney"). Applicant traverses the rejection with respect to the claims where the rejection has not been rendered moot by amendment.

Hale teaches a compound having a pharmaceutical agent ("A") and a chemical modifier ("B"). A "nucleotide-based pharmaceutical agent" and a "nucleotide-based chemical modifier" are two of the literally hundreds[1] of A and B groups, respectively, that one could glean from Hale.

Hale also discloses a functionality modifier ("C") which can be bound to either the pharmaceutical agent, the chemical modifier, or a spacer group (col. 38, lines 33-35). One functionality modifier is naproxen. Naproxen is only mentioned once in Hale (col. 38, line 57), and not in connection with any specific pharmaceutical agent. Moreover, Hale does not disclose ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, or carprofen.

At the broadest, Hale is limited to A+B or A+B+C. When C is present, A and B also must be present as required by C's definition ("A functionality modifier is a chemical entity which possesses at least one chemical functionality which can be covalently bound to the pharmaceutical agent-chemical modifier complex (optionally via a spacer group) ..." (col. 38, lines 18-22)). In citing Hale, the Office action attempts to create an A+C (nucleotide-based

1 Hale's pharmaceutical agent includes hundreds of varied compounds, such as vitamins, minerals, antifungals, analgesics, digitalis drugs, steroidal compounds, nonsteroidal anti-inflammatories, protein and peptide drugs, nucleotide-based drugs, and heterocyclic drugs. Hale also teaches dozens of chemical modifiers, including those that are positively charged, negatively charged, and nucleotide-based.

pharmaceutical agent + naproxen) or perhaps B+C (nucleotide-based chemical modifier + naproxen). However, as stated above, when C is present, A and B also must be present. Thus, Hale requires a third group to be present in addition to an oligomeric compound conjugated to naproxen. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP 2143.01. Such modification of the teaching of the reference is based on impermissible hindsight.

Even assuming *arguendo* that modification of Hale is acceptable, Hale teaches only naproxen. As such, the Office action attempts to combine Hale with Blaschke (which still fails to disclose suprofen, (S)-(+)-pranoprofen, and fenbufen). As discussed in MPEP 2143.01, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. However, nothing in Hale suggests the combination. In fact, the absence of other arylpropionic acids from Hale's disclosure when so many other compounds are disclosed argues against substitution of other arylpropionic acids for naproxen. Likewise, Blaschke is limited to a process for obtaining enantiomers of 2-arylpropionic acids by reacting a racemic mixture thereof with an amine-enantiomer, and has no permissible reason for being combined with Hale.

Herve, Lagrange, and the Applicant's specification teach that arylpropionic acids bind plasma proteins and/or albumin. However, neither Herve nor Lagrange suggest the desirability of this as relates to oligomeric compounds, and thus fails to supply the deficiency of Hale. The mere fact that references can be combined or modified does not render the

resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01.

Blaney is cited to "provide a motivation to extend the half-life of oligonucleotides and polypeptides in serum since is [sic] has been asserted by Blaney et al that it was known in the art that there was such a need." Of course, solving "long felt but unsolved needs" is a secondary consideration in the obviousness analysis. Far from supplying the deficiencies of Hale, Blaney appears in this respect to support patentability of the Applicant's claims. In addition, Blaney fails to teach arylpropionic acids or naproxen.

Reconsideration and allowance is requested. If the Examiner has any questions, he is respectfully invited to call the undersigned.

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